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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant: KUMAR *et al.*

Application No.: 09/888,268

Filing Date: June 22, 2001

Examiner: Micah Paul Young JUN 8 2004

Group Art Unit: 1615

TECH CENTER 1600/2900

Title: **BIOAVAILABLE DOSAGE FORM OF LORATADINE**

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RESPONSE TO OFFICE ACTION DATED JANUARY 27, 2004

In response to the Office Action mailed January 27, 2004, submitted herewith is a Petition for Extension of Time from April 27, 2004 to May 27, 2004. This Petition includes an authorization to charge the required fee.

In view of the following remarks, reconsideration and allowance of this application are requested. Claims 1-18 are pending with claims 1 and 10 being independent.

Claim 1 is directed to a bioavailable oral dosage form of loratadine having a particle size of 0.1 to 15 microns and a surface area of 1 to 2.5 m^2/g.

In the Office Action dated January 27, 2004, the Examiner rejected claims 1-18 as being unpatentable over the combined disclosures of Munayyer et al (WO 99/62516), Ayer et al (USPN 3,980,778) and Liversidge et al (USPN 5,145,684).

According to the Examiner, Ayer discloses a drug formulation containing an active ingredient which can be an antihistamine and the active agent is ball milled to sizes below 5 microns. Munayyer discloses an oral syrup formulation containing loratadine. Liversidge discloses dispensible particles consisting essentially of a crystalline drug substance with a surface modifier absorbed on the surface thereof to maintain an average particle size of less than about 400 nm. The Examiner asserts that one skilled in the art would have been motivated to incorporate the loratadine of Munayyer into the formulation of Ayers utilizing the teachings of Liversidge. Applicants respectfully disagree because there is no suggestion or motivation in the combination of cited references to produce a dosage form of loratadine having a specific particle size and surface area as claimed.

Ayer teaches topical creams and ointments that include a steroid which has been "ball-milled with a little mineral oil to a particle size of less than 5 microns". See Examples A, C, and C1. As is known in the art, the particle size in a topical preparation must be sufficiently small to provide a smooth texture without the gritty feel of larger particles. Thus, Ayer is not ball-milling the steroids of Examples A, C, and C1 to improve their bioavailability but to provide the desired texture of a topical preparation. In fact, contrary to teaching particle size reduction to increase bioavailability or potency, Ayer states that the weight percentage of the steroid can be increased to increase the potency. See Col. 18, lines 50-52.

Although Ayer teaches oral dosage forms, he does not teach oral dosage forms having a particle size that is less than 5 microns. While Ayer's Examples S and T are

oral dosage forms with micronized active ingredient, Ayer does not disclose either a size range of the particles or a surface area of the particles. Instead, only the ointments and creams are stated to have a particle size of less than 5 microns. Thus, contrary to the assertion in the Office Action, Ayer lacks any disclosure or reference to the reduction of particle size in order to increase the bioavailability. In summary, Ayer discloses oral dosage forms but does not disclose the particle size of the active ingredient in them. Although Ayer discloses the particle size of the active ingredient being less than 5 microns in ointments and creams, one skilled in the art would not look to an ointment or cream to teach how to increase the bioavailability of the active ingredient in an oral dosage form.

Munayyer discloses an oral syrup formulation that includes micronized loratadine, fillers, binders and lubricants. See Examples 1-5. The reference fails to define the particular particle size and/or surface area of the "micronized" loratadine. In addition, several examples utilize different active ingredients, all of which are not micronized, so there is no indication that micronization is necessary or even the preferred form. See Examples 6-9. Although loratadine is disclosed in Munayyer, the teachings are directed to increasing stability and limiting degradation of the drug substance; nowhere is there a general discussion related to increasing the bioavailability. See Page 5, lines 1-5. Without a disclosure suggesting the importance or utility of the micronization of the active ingredient by decreasing the particle size and increasing the surface area, Munayyer fails to motivate one skilled in the art to combine this reference with Ayer.

Liversidge discloses particles of a crystalline drug substance having a surface modifier absorbed on its surface in order to maintain an effective average particle range of less than about 400nm and a process for their preparation. See Col. 5, lines 13-19. Liversidge teaches that in order to limit flocculation and agglomeration of the particles,

which subsequently would increase the particle size and decrease the surface area, surface modifiers are necessary to function as a mechanical or steric barrier. See. Col. 21-26. Additionally, it is disclosed that "not every combination of surface modifier and drug substance provides the desired results." See Col. 7, lines 21-23. Although Liversidge discloses a composition useful for decreasing the particle size of a drug substance, there is no indication that this type of milling can be accomplished without a surface modifier or with loratadine as the drug substance, as is done in the present invention. Applicants respectfully submit that Liversidge would not suggest or motivate one skilled in the art to combine this reference with Ayers or Munayyer.

Alternatively, even in light of prima facie obviousness, the evidence of unexpected and superior results in bioavailability over the commercially available formulations of loratadine is sufficient to warrant overturning the rejection (See Table 4.2, page 8 and is reproduced below).

Table 4.2

	$AUC_{(0-t)}$	$AUC_{(0-\alpha)}$	C_{max} (μg/ml)
Test/ Reference (%)	134	124	130

Considering that one skilled in the art would assume the expected bioavailability results to parallel the bioavailability of the commercial product, the present results are evidence of an unexpected and superior 30% increase above the commercial product. When weighed against the evidence supporting prima facie obviousness, this objective statistical improvement carries much weight. For this reason, as well as the arguments presented above, Applicants respectfully request that this rejection over claim 1 and dependent claims 2-9 be withdrawn.

Independent claim 10 is directed to a method of making an oral dosage form containing loratadine. Like claim 1, claim 10 recites a formulation of loratadine having a particle size of 0.1 to 15 microns and a surface area of 1 to 2.5 m^2/g. As such, claim 10 and dependent claims 11-18 are allowable over Munayyer, Ayer and Liversidge for the same reasons that claim 1 is allowable.

In light of the foregoing, Applicants submit that this application is in condition for allowance and respectfully request consideration thereof.

Conclusion

For the reasons stated above, the Examiner is urged to pass claims 1-18 to issue immediately. Authorization is hereby given to charge any fees deemed to be due in connection with this Response to Office Action to Deposit Account No. 50-0912.

Respectfully submitted,

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